A CLINICO PATHOLOGICAL STUDY OF GLIOMAS

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CERTIFICATE

This is to certify that this dissertation entitled **"A CLINICO PATHOLOGICAL STUDY OF GLIOMAS"** is a bonafide work done by Dr. S. PREMALATHA, in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

DIRECTOR
Prof. Dr. A.V. SHANTI, M.D.,
Director and Head
Institute of Pathology &
Electron Microscopy
Madras Medical College
Chennai-600003

GUIDE
Prof. Dr. SHANTHA RAVISHANKAR
M.D., D.C.P.,
Professor of Neuropathology
Institute of Pathology &
Electron Microscopy
Madras Medical College
Chennai-600003

DEAN
Prof.Dr.Kalaniti,M.D.,
Madras Medical College & Government General Hospital
Chennai - 600003.

DECLARATION

I declare that this dissertation entitled **"A CLINICO PATHOLOGICAL STUDY OF GLIOMAS"** has been done by me under the guidance and supervision of Prof. **Dr. SHANTHA RAVISANKAR, M.D.** It is submitted in partial fulfillment of the requirements for the award of the M.D., Pathology degree by The Tamil Nadu Dr. M.G.R. Medical University, Chennai. This has not been submitted by me for the award of any degree or diploma from any other University.

Dr. S. PREMALATHA.

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INTRODUCTION

Brain tumors are among the common neoplasms of humans. Primary central nervous tumors are the 6th most common tumors in adults. Patients tend to concentrate in institutions where diagnostic and the therapeutic services are available. The incidence of brain tumors is around 5-6/1,00,000 population. Supratentorial brain tumors constitute about 80% of brain tumors in adults and 40% of tumors in paediatric population. Brain neoplasms are found in 2% of autopsy series and account for 1% of all the hospital admissions.[31]

Gliomas are the most common primary tumors of the CNS and represent approximately one third of all the intracranial tumors in adults. The therapeutic management and prognosis in patients with gliomas depend on the reliable distinction between low and high grade gliomas.

Diagnosis of brain tumors may be delayed as the initial symptoms and signs are vague and non specific. The symptoms include headache, focal seizures and focal neurological deficits with clinical examination revealing raised intracranial tension or focal neurological deficits.

Therefore the clinicians rely heavily on imaging for an early and accurate diagnosis. Both CT and MRI provide excellent anatomical details and information regarding the presence, location and extent of brain tumors.

Computed tomography is the baseline imaging modality to evaluate patient with gliomas. Although CT scan has proved to be an effective method for the diagnosing supratentorial tumors, infiltrative lesions with attenuation similar to normal structure may not be imaged unless they are large enough to cause significant mass effect. Superficially situated tumors are also often obscured by artifacts caused by calvaria. It is estimated 11.5% of hemispheric tumors are not demonstrated by CT.[1]

The neurosurgical care and prognosis of patients with cerebral gliomas depend on the accurate definition of tumor grade. The imaging characteristics of gliomas are not specific enough to obviate the need for biopsy.[1]

AIM OF THE STUDY

1. To study the distribution of various subtypes of gliomas with regard to age, sex and site

2. Histopathological categorization of gliomas and grading them as per the WHO 2000 classification of central nervous system tumors.

3. To correlate the radiological findings with the histopathological grading of gliomas.

MATERIALS AND METHODS

The study comprised of 110 patients of which 73 were males and 37 were females ranging from 1 to 65 years. The study was conducted from May 2005 to August 2007.

The patients were from Institute of Neurology, Government General Hospital, Chennai-3, Institute of child Health, Egmore, Chennai-8 and the study was conducted in the Department of Neuropathology, Madras medical College, Chennai-3.

Inclusion criteria:

Patients diagnosed to have gliomas by imaging studies and who were subsequently operated.

Exclusion criteria:

1. Patients unable to provide informed consent.
2. Women of childbearing potential
3. Patients with significant hepatic or renal dysfunction.

CT was done with Toshiba X SPEED Third generation scanner machine. Axial study with contrast was performed in all cases and the contrast used was 60 ml of Iohexol.

MRI was performed using 1.5 Tesla superconducting SIEMENS MAGNETOM. T1 WI, T2 WI and FLAIR sequence was done. Contrast study was done in all cases using 0.1mmols/kg of Dimeglumine Gadopentilate.

The specimens received after the surgery were fixed in 10% buffered formalin and manually processed. Gross features like size, shape, colour, consistency, cystic and necrotic changes were noted. The tissues were mostly in fragments. Wherever possible the specimens were bisected longitudinally and a minimum of four bits each measuring 3 to 5 mm thickness was taken. After manual processing sections of 3 to 5 microns thickness were cut and stained with hematoxylin and eosin.

PROCEDURE FOR HEMATOXYLIN AND EOSIN STAINING[36]

1. Dewax the section, dehydrate through graded alcohols and bring sections to water.
2. Remove fixation pigments if necessary, stain in Harris Hematoxylin for 5 minutes.
3. Wash well in running tap water.
4. Differentiate in 1% acid alcohol for 2- 4 seconds.

5. Wash well in running tap water until sections are blue again for 15 – 20 minutes.
6. Stain in eosin for one minute
7. Wash in water for 5 minutes
8. Dry the sections, clear in xylene, mount with DPX, and label the slide.

For interpretation and correlation the following aspects of gliomas were studied and analysed.

1. Age and sex
2. Site of the tumor
3. CT characteristics:

    Density

    Calcification

    Mass effect

    Contrast enhancement

4. MRI characteristics:

    T1 signal intensity

    T2 signal intensity

FLAIR

Contrast enhancement

5. Histopathological features

Cellularity

Nuclear pleomorphism

Mitosis

Giant cells

Necrosis

Endothelial proliferation

Calcification

The gliomas were subtyped into various histological grades as per the WHO 2000 classification of Central Nervous System tumors. Mixed papillary ependymoma, subependymoma and ependymoma with spinal localization were excluded from the analysis because these tumours if included confounded the results.

REVIEW OF LITERATURE

Gliomas of astrocytic, oligodendroglial and ependymal origin account for more than 70% of all brain tumors.

The most frequent (65%) and most malignant histologic subtype is the glioblastoma. Since the introduction of computerized tomography and magnetic resonance imaging, the incidence rates of brain tumors have been rather stable.[20]

The parenchyma of the CNS is composed of primarily of neurons and glia. In turn the glia is composed of 3 types of cells, astrocytes, oligodentrocytes and ependymal cells. While neoplasms can arise from either the neuronal or glial components of the CNS, the glial tumors are by far more important both in terms of frequency and clinical aggressiveness.

CLASSIFICATION OF CNS TUMORS

The attempt to classify tumors of nervous system has a history of nearly 150 years. The initial major classification system was published in 1926 by Percivial Bailey et al neuropathologist working with neurosurgeon Havey Cushing et al.[2]

This classification divided tumor types into 14 groups, with medulloepithelioma arising from medullary epithelium giving rise to all

other malignant neoplasms. In this hierarchical classification system, medulloepithelioma differentiated into pineoblastoma, ependymoblastoma, spongioblastoma multiforme (glioblastoma multiforme),medulloblastoma and neuroblastoma. The most differentiated neoplasms – pinealoma, ependymoma, astrocytoma fibrillae and astrocytoma protoplasmaticum, oligodendroglioma and ganglioglioma and choroids plexus papilloma were at the base chart with choroid plexus papilloma arising directly from medulloepithelioma. Bailey and Cushing et al.[3] also established an expected clinical outcome for each tumor type in their classification scheme.

Oligodendroglioma was initially considered a differentiated form of medulloblastoma. The classification system was simplified in the next few years when Bailey and Bucy et al[4] using the histological staining technique developed by del Rio Horteja**,** proved the presence of oligodendrocytes in oligodendrogliomas and reclassified these tumors of glial cell lineage. Bailey et al made further changes, combining the two astrocytic tumors, eliminating the categories of medulloepithelioma, ependymoblastoma and neuroblastoma, noting that choriod plexus papilloma was not usually considered a glioma.

Kernohan & Sayre et al[26] classified tumors into 5 subtypes – astrocytoma, oligodendroglioma, ependymoma, gangliocytoma &

medulloblastoma and more importantly added a grading system. Russell and Rubinstein et al[38] considered Kernohan's system oversimplified because of omission of certain rare but real tumors such as neuroepilthelioma and polar spondioblastoma. They also believed tumors should be graded based on postmortem examination, when large sample could be analysed.

Under the auspices of the WHO, neuropathologists met twice in the 1970's and developed a new classification and grading system for brain tumors, which Zulch et al published in 1979.[53] The classification system was to be comprehensive, clarify existing controversies in tumor typing, provide a histological grading system across a variety of intracranial neoplasms and provide a means of communication between neuropathologists, neurosurgeons, neuro-oncologists, radiation oncologists and other health professionals involved in the treatment of brain tumors. Kleihuer, Burger and Scheithauer et al[27] after two international working group meetings in 1988 and 1990 revised the system in 1993.

The introduction of the second edition of the WHO classification system takes the compromise position that grading is not necessary for tumor typing but if a grading system is used it should be identified.

The current international histological classification of CNS tumors drafted in 2000 revision by the WHO has been adapted and modified from Kleihuer P Caverer W.K et al .[32]

WHO CLASSIFICATION OF GLIOMAS [53]

ASTROCYTIC TUMORS	ICD-O CODE
Diffuse astrocytomas	9400/3
Fibrillary astrocytomas	9420/3
Protoplasmic astrocytomas	9410/3
Gemistocytic astrocytomas	9401/3
Glioblastoma	9440/3
Giant cell Glioblastoma	9441/3
Gliosarcoma	9442/3
Pilocytic astrocytomas	9421/1
Pleomorphic xantho astrocytomas	9424/3
Subependymal giant cell astrocytomas	9384/1
OLIGODENDROGLIAL TUMORS	
Oligodendroglioma	9450/3
Anaplastic Oligodendroglioma	9451/3
MIXED GLIOMAS	
Oligoastrocytomas	9382/3

Anaplastic Oligoastrocytomas	9382/3

EPENDYMAL TUMORS

Ependymoma	9391/3
Cellular Ependymoma	9391/3
Papillary Ependymoma	9393/3
Clear cell Ependymoma	9391/3
Tanycytic Ependymoma	9391/3
Anaplastic Ependymoma	9392/3
Myxopapillary Ependymoma	9394/1
Subependymoma	9383/1

ASTROCYTOMA

Astrocytoma is the most common primary CNS tumor. The term astrocytoma was used as early as the late 19th century by Virchow et al but was firmly introduced and histopathologically classified in 1926 by Bailey and cushing et al.

Many grading systems have been frequently used in describing astrocytomas. The kernohan system introduced in 1950 by Kernohan and Sayre et al[26] divided astrocytomas into grade I to IV with increasing malignancy. Grade III and IV astrocytomas were called glioblastomas and

both contained mitosis, endothelial proliferation and necrosis. A sharp distinction did not exist between them using these grades.

In 1950, Ringertz et al [35] developed a three tiered system of astrocytoma, anaplastic astrocytoma and glioblastoma multiforme using increasing vascular proliferation and necrosis as criteria for increasing malignancy.

In 1979, the first WHO classification was developed by Zulch et al.[53] To develop a reproducible grading system, Doumas Duport et al and colleagues proposed a discrete grading system based on the presence or absence of nuclear atypia, mitosis, endothelial proliferation and necrosis in pathological specimen and termed it as St Anne/Mayo system. If no criteria is present the tumor is classified as grade I, if one criteria, grade II, if two criteria, Grade III and if 3 or 4 criteria are present then its grade IV.

Glioblastoma was identified by Virchow in 1863 as being of glial origin, but it took several decades by Strauss and Globus et al[46] to give the first comprehensive description of this tumor. A detailed histological account was given by Zulch[53], Russell and Rubinstein et al.[38] In the 1st edition of WHO classification of tumors of CNS glioblastoma was grouped with the medulloblastoma in the category termed poorly differentiated and embryonal tumors. It was probably the introduction of GFAP

immunohistochemistry that finally confirmed its origin from differentiated astrocytes. Scherer et al[40] in 1940 first introduced the term primary and secondary glioblastomas.

A COMPARISION OF PATHOLOGIC GRADING SYSTEM COMMONLY USED IN ASTROCYTOMAS[18].

Kernohan	Ringertz 1950	WHO 1979	UCSF 1989	Mayo/ St.Anne 1993	WHO 1993	WHO 2000
Grade I			Mildly anaplastic	Grade I		Pilocytic astrocytoma
Grade II	Astrocytoma	- do -	Mildly anaplastic	Grade II	Astrocytoma or anaplastic astro	Diffuse astrocytoma
Grade III	Anaplastic astrocytoma	- do -	Moderately anaplastic	Grade III	GBM	Anaplastic astrocytoma
Grade IV	GBM	GBM	GBM	Grade IV	GBM	GBM

Pilocytic astrocytoma was initially discussed in 1918 by Ribbert. Bailey and Cushing et al[3]included it in their initial brain tumor classification in 1926, under the name spongioblastoma.

In 1931, Penfield et al[33] called these tumors piloid astrocytoma to describe the elongated bipolar and multipolar cells.

Kagan and Rubinstein et all[38] named the same tumor astrocytoma of juvenile type because of the age group in which it occurred and to differentiate it from the more malignant glial neoplasms. The 2000 WHO classification system groups all piloid tumors with the biphasic pattern as pilocytic astrocytoma.

Kepes et al[24] described a relatively rare but well recognized variant of cerebral astrocytoma and called it Pleomorphic Xanthoastrocytoma.

OLIGODENDROGLIOMA

In general most of the grading schemes divide oligodendroglial tumors into low grade and high grade lesions (two - tier systems). Accordingly, the WHO distinguishes two grades: WHO grade II corresponding to oligodendroglioma and oligoastrocytoma and WHO grade III corresponding to anaplastic oligodendroglioma and anaplastic oligoastrocytoma.

The Smith grading system separates oligodendroglial tumors into four groups based on assessment of endothelial proliferation, necrosis, nuclear cytoplasmic ratio, high cell density and pleomorphism - notably omitting mitotic activity as a major variable.

The Kernohan grading scheme and the St.Anne Mayo grading scheme can also be applied to oligodendrogliomas and show correlation with survival.

A two grade scheme as also been proposed by Daumas Deport et al[11] that incorporates neuro imaging features as well as histology. Grade A tumors are characterized by absence of endothelial hyperplasia and/or contrast enhancement on imaging while grade B tumors are characterized by endothelial hyperplasia and/or contrast enhancement on imaging. Median survival for grade A lesion was 11 years while that for grade B lesion was 3.5 years. The presence of microvascular proliferation was correlated with survival in this series while nuclear atypia, necrosis and mitosis were not predictive of survival.

Mixed Oligoastrocytomas were first recognized as an entity by Cooper[10] in 1935.

EPENDYMOMA

Virchow et al published the first description of an ependymoma in Germany in the 1860's during the American civil war. In 1924, Bailey et al first classified ependymomas as glial tumors and in 1926, Bailey and

Cushing et al[3] developed the histological classification of brain tumors with primitive spongioblast as the cell of origin. Ependymomas were the more differentiated tumors of this classification.

Kernohan and Fletcher et al[26] studied 108 cases of ependymomas and classified the tumors according to their histological types as epithelial, myxopapillary and cellular.

IMAGING MODALITIES

A variety of imaging modalities have been evaluated in accurate identification of glioma grade and clinical characteristics.

Tumor imaging has changed dramatically since 1970. The modern era of CNS imaging began in 1973 with introduction of computed tomography by Oldendorf and Hounsfield et al.

CT was the first brain imaging method to determine the tumor size. Baker et al[5,6] reviewed the impact of CT in the diagnosis of brain tumors and found that it significantly altered the method and timing of diagnostic evaluation of the patients with suspected brain tumors. The areas of structural abnormality eg., tumors appeared on CT as regions of altered tissue radiographic density.

CT is the baseline imaging modality to evaluate patients with gliomas. Newer multislice helical or spiral CT scanners are capable of providing highly collimated submillimeter thickness sectional images in extremely short acquisition time and thus intra tumor calcification, early intratumoral and peritumoral hemorrhage and bone destruction are more completely defined with great certainty on CT. CT remains a major imaging technique for the follow up study of intra cranial lesion.

The development of magnetic resonance imaging fostered a clinical partnership among neurologist, neurosurgeon, neuroradiologist and radiation oncologist for the interpretation of the same.

MRI, the static imaging procedure of choice for brain tumors was developed in the mid 1980's. Damadrin and Hindshaw et al, in 1980 demonstrated the multiplanar facility of MRI and reported the first demonstration of intracranial pathology using MRI.

MRI with or without gadolinium is the procedure of choice for the initial diagnostic imaging of patients, suspected of having an intracranial primary brain neoplasm. Zimmerman and Prince et al[34, 51] found that MRI was more sensitive compared to CT in lesion identification.

Fluid attenuation inversion recovery (FLAIR) scans, T2 weighted MRI are the two most useful scans. The margins of the T2 weighted abnormality are a more accurate marker of the primary glioma boundary.

Dean et al[13] introduced a MRI scoring system based on 7 criteria for the non invasive grading of astrocytomas. This scoring system was later modified by Asan et al who incorporated the following 9 criteria: heterogeneity, cyst formation or necrosis, hemorrhage, tumor crossing the midline, edema and/or mass effect, definition of border, flow void, degree of contrast enhancement. They suggested that it may be possible to differentiate low grade astrocytoma easily from high grade astrocytoma on MRI by using MRI scoring system using the 9 criteria. It was inferred that 5 out of 9 criteria were significantly lower in low-grade gliomas than in high-grade gliomas. These criteria were heterogeneity, cyst formation or necrosis, edema and/or mass effect, definition of border, degree of contrast enhancement.

R. Ashok Kumar and Niranjan Khendelwal et al[1] conducted a study and applied MRI scores to both astrocytomas and oligodendrogliomas. The data revealed significant difference between the mean MRI scores of low grade (Grade I-II) and high grade (grade III-IV) yielding the maximum accuracy with 0.9 as the mean MRI score. By using this threshold, contrast

enhanced MRI enabled correct identification of tumor grade in 15 patients, 3 low grade gliomas were graded as high grade gliomas and one high grade glioma was graded as low grade glioma. This corresponded to a sensitivity of 90%, specificity of 66.66% and overall accuracy of 78.94%.

Thus an effective MRI scoring system for grading can be formulated for all gliomas including astrocytomas, oligodendrogliomas and mixed glial tumors.

The current reference standard for determining glioma grade is histopathological assessment according to the Joint Section on Tumors of the American Association of Neurological Surgeons/Congress of Neurological Surgeons. However the limitations of histopathology obtained are well known because

1. Only a few small samples of tissue are assessed particularly from stereotactic biopsy, the most malignant portion of the tumor may not be sampled (sampling error).
2. It may be difficult to obtain a range of sample if the tumor is inaccessible to the surgeon.
3. There are numerous classification/grading systems between different institutions.
4. Interpathologist and intrapathologist variability.

5. The dynamic nature of CNS tumor with at least 50% dedifferentiating into more malignant grades.

STEREOTACTIC BIOPSY

Surgery for neoplasms within the brain and its surrounding structures has evolved over the past 100 years. The advent of the operating microscope in the 1970's and computerized imaging and guidance in the 1990's have provided significant technical advances in surgical technique. In 1884 Bennet and Godlee et al[7] performed the first successful resection of a brain tumor that has been localized by neurological examination and the lesion was a low grade tumor.

In the mid 1990's Spetzegar U and Laborde G et al[45] used sophisticated frameless stereo tactic devices for the better intra operative localization. The operative microscope was brought into clinical use in the neurosurgical operating room in the 1970's originally for the vascular lesions. It has now become standard operating tool for many surgical approaches to brain tumors.

Franklin Earnest W, Patrick J, Kelly et al[16] conducted a study on the histopathological correlation of MRI and CT contrast enhancement with stereo tactic biopsy in six selected patients with brain tumor and inferred that

regions of contrast enhancement demonstrated by CT and MRI in 4 out of 6 patients correlated with areas of malignant neovascularity and endothelial proliferation within solid tumor.

The value of intra operative diagnosis of brain tumors was studied by Tilgner J, Here M et al.[50] A retrospective analysis and regression analysis of 4589 consecutive stereo tactic biopsies from 5000 patients was analysed and was found that histopathological diagnosis is an important tool in neuro-oncology despite improvement in imaging technique. A high correlation was found for WHO type II astrocytomas and with regression analysis for WHO type I astrocytomas, glioblastomas and metastasis from this study.

ETIOLOGY OF GLIOMAS

Analytical epidemiological studies have revealed an increased risk of gliomas in association with a variety of conditions but attempts to unequivocally identify a specific causative exposure or environmental agent have so far been unsuccessful with the exception of therapeutic irradiation.

There is accumulating evidence that a significant fraction of human neoplasms including brain tumors contain DNA sequences identical to SV40 large T antigen. In astrocytic tumors, this occurs at a frequency of up to 50%[21]. A recent study reported the presence of sequences from SV40 virus

in 3 of 12 oligodendrogliomas. More recently natural SV40 strains have been identified in human ependymomas.

Familial clustering of gliomas is not uncommon. The association with defined inherited tumor syndromes includes the Li-Fraumani syndrome, Turcot syndrome, Tuberous sclerosis, neurofibromatosis (NF1) and multiple enchondromatosis (Maffuci/Ollier's disease).

LOW GRADE GLIOMAS

DIFFUSE ASTROCYTOMA (WHO Grade II)

Diffuse astrocytoma are slow growing, diffuse, well differentiated tumors. They arise most commonly in the cerebral hemispheres of young adults, aged 20-40 years, but also occur in the pons, medulla and spinal cord particularly in children and adolescents.

It constitutes 10% of primary cerebral tumors. Diffusely infiltrating astrocytomas are the most frequent CNS neoplasm and account for more than 60% of all brain tumors.

Low grade astrocytomas typically affect young adults, while glioblastoma shows a peak incidence in the 6^{th} decade. Anaplastic astrocytomas occupy an intermediate position. Males are most commonly affected.

Because of their infiltrative nature, these tumors usually show blurring of the gross anatomic boundaries. There is enlargement and distortion, but not destruction of the invading anatomical structures.

Microscopically three major cytological patterns are observed in diffuse astrocytomas.

1. Fibrillary astrocytomas
2. Protoplasmic astrocytomas
3. Gemistocytic astrocytomas

Fibrillary astrocytoma is the commonest type of histological pattern seen in diffuse astrocytomas. Cell density is low to moderate. The cytoplasm is scanty. Nuclear atypia or irregular hyperchromatic nuclei are a histological hallmark distinguishing normal and reactive astrocytes. Microcyst is a characteristic feature (fig 4).

Protoplasmic astrocytoma is a rare variant characterized by neoplastic astrocytes showing a small cell body with few thin processes with a low content of glial filaments.

Gemistocytic astrocytoma in its pure form is an uncommon subtype of diffuse astrocytoma. Gemistocytes (fig. 6,7) should amount to more than approximately 20% of all tumor cells. Gemistocytes are characterized by plump, glassy, eosinophilic cell body of angular shape. Stout, randomly

oriented processes form a coarse fibrillary network. Buger PC, Vogel T et al reported the presence of perivascular cuffing.[8] This variant appears to be particularly prone to progress to anaplastic astrocytoma and glioblastoma.

CT shows an ill defined homogenous hypodense/isodense mass with no or very minimal enhancement. Enhancement should raise the suspicion of focal malignant degeneration.

In MRI T1 weighted sequence shows a homogenous hypointense mass with surrounding edema rarely. T2 weighted sequence and FLAIR show a homogenous hyperintense mass.

PILOCYTIC ASTROCYTOMA (WHO Grade I)

Pilocytic astrocytoma is the most common gliomas in children represent 10% of cerebral and 85% of cerebellar astrocytomas.

Grossly in the cerebellum, the pilocytic astrocytoma is well delineated and appears to expand rather than infiltrate into adjacent brain structures. At other sites the border with adjacent structures is less defined. The cut surface is grayish-pink and often shows mucoid degeneration leading to the formation of cysts, a hallmark present in more than 80% of cerebellar astrocytomas.

Microscopically two distinct varieties exist, the juvenile form described by Russel and Rubenstein et al and the adult variant described by

Clarke et al. most pilocytic astrocytomas have biphasic histological pattern (fig. 1) with areas of pilocytic cells and microcystic areas containing stellate cells with defined processes.[38] Both types of cells contain glial fibrils. The adult variant has monotonous areas of densely packed broad bipolar without microcystic areas. Rosenthal fibres (fig 2), eosinophilic granular bodies (fig.3) are often seen.

CT demonstrates discrete cystic/solid mass with little or no surrounding edema. Mural nodule can be seen within the cysts. More than 95% of them enhance with contrast. T1 weighted images show iso to hypointense areas while T2 weighted images shows hyperintense areas.

PLEOMORPHIC XANTHOASTROCYTOMA (WHO Grade II)

This accounts for less than 1% of astrocytic tumors. 98% of tumors arise above the tentorium with a proclivity for the temporal lobe.

Grossly cystic and solid components are made out. Cystic spaces may be quite conspicuous containing voluminous dark golden, xanthochromic serous fluid. The mural nodule is of varying colour, with a predominant yellow-orange hue.

The most striking histopathological features are multinucleated and lipidized giant cells (fig. 17) with bizarre, often hyperchromatic nuclei. In addition, there are small round/polygonal and fusiform cells often arranged

in fascicular patterns. Tumors with prominent vasculature have been termed as angiomatous variant by Sugita Y, Kepes JJ et al.[47]

CT shows cystic/solid mass which is hypodense with mixed density mural nodules, the nodules shows strong enhancement with contrast (fig.VIIa,b).

T1 weighted image shows hypointense or isointense mass while T2 weighted image shows hyperintense or mixed signal intensity mass.

OLIGODENDROGLIOMA (WHO Grade II)

The important feature of oligodendroglioma is the dominant presence of cells which cytologically resemble normal oligodendrocytes. Oligodendrogliomas represent less than 5% of all primary CNS tumors. Helseth A, Mork S J et al have found that the incidence of the tumor is 7.9% of all gliomas.[19]

These tumors arise between the ages 35 to 55 with the peak around 45 years. Male to female ratio is 1.5 to 2:1 according to Zulch K et al.[52]Most of the oligodendrogliomas arise in the periphery of the cerebral hemispheres in the frontal, parietal, temporal, occipital lobes in the ratio of about 3:2:2:1.

Grossly they are typically solid, soft, tan to pink colour tumors. Some lesions have a gelatinous texture which has been related to accumulation of extracellular mucopolysaccharides within the tumor[15]. Appearance of a

single expanded gyrus is highly characteristics of oligodendroglioma. Calcification is seen macroscopically in about 50% of these tumors.

Microscopically oligodendrogliomas are composed of glial cells with uniform rounded or slightly oval shaped nuclei, small amount of cytoplasm and small number of cell processes. Perinuclear halo, highly characteristic of oligodendroglioma is probably related to autolytic cytoplasmic vacuolations. Blood vessels are typically numerous, thin walled, straight and branching segments and small arcs likened to "chicken wire" (fig. 8). Astrocytic cells and mini gemistocytes along with calcification are typical of these tumors.

CT shows a mixed density mass with nodular or clumped calcifications. Around 50% of these tumors enhance with contrast.

In MRI T1 weighted images shows a hemispheric mass which is hypo to isointense mass with typically heterogeneous. T2 weighted images and FLAIR shows heterogeneous, hyperintense mass with occasional cystic changes. Heterogeneity is related to the calcium present in the tumor.

OLIGOASTROCYTOMA (WHO Grade II)

The estimated incidence of this tumor varies and represents no more than 10 to 20% of supratentorial low grade gliomas. In an analysis of 4859 patients with different histological types of intracranial gliomas registered by the Norwegian Cancer Registry between 1956 and 1984, 9.2% were

mixed gliomas.[19] Males are affected slightly more frequently than females with the ratio of 1.2:1. The frontal lobes are most commonly affected followed by the temporal lobe.

Histologically the diagnosis of oligoastrocytomas requires the recognition of two different glial components both of which must be unequivocally neoplastic. The tumors in which a clear fibrillary, protoplasmic or classic gemistocytic astroglial component is evident in addition to the oligodendroglial cells are diagnosed as oligoastrocytomas (fig. 9). The presence of neumerous mini gemistocytes should raise the suspicion of oligoastrocytomas and a search for astrocytic component has to be made.

Neuroradiologically, oligoastrocytomas demonstrate no special features that would allow a reliable distinction from WHO Grade II oligodendrogliomas. In the series of Shaw et al about half of the oligoastrocytomas evaluated by CT scan showed contrast enhancement and calcifications were demonstrable in 14% of the tumors.[42]

EPENDYMOMA (WHO Grade II)

Ependymomas account for 3 to 9% of all neuroepithelial tumors. They amount to 6 to 12% of all intracranial tumors in children, and to 30% of those in children younger than 3 years. In the spinal cord ependymomas are

the most common neuroepithelial neoplasms, comprising 50 to 60% of spinal gliomas.[41] Ependymomas may develop in all age groups with a range from one month to 81 years. They most commonly develop in the posterior fossa and in the spinal cord, followed by the lateral ventricle and the third ventricle.

Grossly they are typically reddish grey in colour and form nodular or lobulated mass with some of them showing cystic elements, necrosis or hemorrhage.

Microscopically ependymomas are well delineated moderately cellular gliomas with a monomorphic nuclear morphology. The key histological features are perivascular pseudo-rosette (fig. 10) and ependymal rosettes. True ependymal rosettes are relatively uncommon and are most often encountered in the posterior fossa tumors in younger age group, where it is claim to have a poor prognosis.[22] Focal calcification may be present especially in those located supratentorially.

In supratentorial ependymomas CT shows large heterogeneous periventricular mass with variable heterogeneous enhancement with contrast. Calcification is seen in about half of these cases. Both T1 and T2 weighted images show a heterogeneous, usually iso to hypointense mass.

FLAIR sequences show a sharp interface between the tumor and CSF. Mild to moderate, heterogeneous enhancement is seen with contrast studies.

HIGH GRADE GLIOMAS

ANAPLASTIC ASTROCYTOMA (WHO Grade III)

Anaplastic astrocytoma can be defined as a tumor which was initially a diffuse astrocytoma but has undergone anaplastic changes. The anaplastic change may be focal and is characterized by;

1. Rapid deterioration in the clinical state of a patient with a diffuse astrocytoma.
2. Focal enhancement on CT or MRI in an otherwise diffuse non enhancing astrocytoma.
3. On biopsy by the presence of anaplastic cells in an astrocytic tumor with high nuclear:cytoplasmic ratio, increased mitotic activity and raised Ki67/MIB-1 proliferation index.

According to Zurich et al the mean age at which anaplastic astrocytomas occur is approximately 41 years. Males are frequently affected.

As with diffuse astrocytomas, anaplastic astrocytomas arise mainly in the cerebral hemispheres.

Grossly the higher cellularity of the anaplastic astrocytoma produces a discernable tumor mass with a clearer distinction from surrounding brain structures. As in diffuse astrocytoma, there is a tendency to infiltrate without frank tissue destruction. This often leads to a marked enlargement of invaded structures.

Microscopic features are those of a diffusely infiltrating astrocytoma with increased cellularity, distinct nuclear atypia (fig. 11,12) and marked mitotic activity. The anaplastic areas are identified by the crowding together of tumor cell nuclei. Due to the relative lack of cytoplasm, many of the nuclei are rod shaped and hyperchromatic. On rare occasions small regions of infarct like necrosis may be found in anaplastic astrocytomas in the absence of highly cellular tumor.

According to Burger PC and Vogel et al, the presence of necrosis would indicate a diagnosis of glioblastoma.[8] CT findings show a low density ill defined mass and with contrast an enhancement often focal, patchy and heterogenous.

In MRI, in T1 weighted images mixed isointense to hypointense mass is seen. In T2 weighted images hererogenous hyperintense mass is seen. In FLAIR also hererogenous hyperintense mass is seen.

ANAPLASTIC OLIGODENDROGLIOMA (WHO grade III)

The percentage of anaplastic tumors among all oligodendroglial tumors varies between 15 to 20%*. These tumors manifest in adults with a slight male predominance. They share with WHO grade II oligodendrogliomas a preference for the frontal lobe (60% in the Dusseldorf series) followed by the temporal lobe (33%).

Grossly they are soft masses of grayish-pink colour with areas of necrosis. Histologically a high cell density, moderate pleomorphism with anaplastic nuclei, prominent mitotic activity, microvascular proliferation and necrosis are seen.

CT shows a heterogeneous pattern, owing to the variable presence of necrosis, cystic degeneration, intra tumoral hemorrhages and calcification. Contrast enhancement on CT and MRI is usual and may be patchy or homogeneous. Ring enhancement is uncommon and when present heralds a poor prognosis.

ANAPLASTIC EPENDYMOMA (WHO Grade III)

It is a type of malignant glioma of ependymal origin with accelerated growth and unfavourable clinical outcome, particularly in children. They are more frequent in intracranial ependymomas, particularly posterior fossa. These tumors exhibit a high mitotic activity often accompanied by microvascular proliferation and pseudo-palisading necrosis.

The features associated with increased likelihood of malignancy in ependymomas:[22]

1. Posterior fossa or large intracerebral tumors in childhood.
2. Epithelial pattern with tubular-rosettes.
3. Significant mitotic rate.
4. Cytological pleomorphism.
5. Vascular endothelial proliferation.
6. Tumor necrosis
7. Diffuse infiltration of adjacent brain tissue.

GLIOBLASTOMA MULTIFORME (WHO Grade IV)

Glioblastoma is the most malignant astrocytic tumor and accounts for 12-15% of all intracranial tumors. Glioblastomas frequently develop from low grade or anaplastic astrocytomas (secondary glioblastoma), but may also arise denovo (primary glioblastoma). It may manifest at any age, but preferentially affects adults, with a peak incidence between 45 and 75 years. They occur most often in the subcortical white matter of the cerebral hemisphere. Glioblastoma of the brain stem are infrequent and often affects children, while cerebellum and spinal cord are rare sites for this neoplasm.

Grossly they are poorly delineated, the cut surface showing a variable colour with peripheral grayish tumor masses admixed with necrosis and hemorrhage.

Histopathology of glioblastoma is extremely variable. The presence of highly anaplastic glial cells, multinucleated tumor giant cells, mitotic activity, microvascular proliferation and/or necrosis is required for the diagnosis of glioblastoma. Burger PC, kleihuer P et al found that poorly differentiated fusiform, round or pleomorphic cells may be seen atleast focally. This occurs in glioblastomas resulting from the progression of diffuse Astrocytomas.[8] Large ischemic necrosis and pseudopalisading necrosis are hallmark of primary glioblastoma. Del Bigio MR & Harris et al have reported large granular cell with granular PAS positive cytoplasm occurring scattered within the glioblastomas.[14] Kepes JJ, Mark SJ et al have reported adenoid and squamous epithelial metaplasia in glioblastoma,but found it to be more frequent in gliosarcoma.[24]

CT shows an irregular isodense/hypodense mass with marked mass effect and surrounding edema. 95% of these tumors are strong, heterogenous, irregular rim- enhancement. T1 weighted image shows an irregular hypointense mass while heterogeneous/hyperintense mass with adjacent tumor infiltration is seen in T2 weighted images.

GIANT CELL GLIOBLASTOMA (WHO Grade IV)

It is a histological variant of glioblastoma with a predominance of bizarre, multinucleated giant cells. This rare variant usually occurs in younger age group. They are often located subcortically in the temporal and parietal lobes.

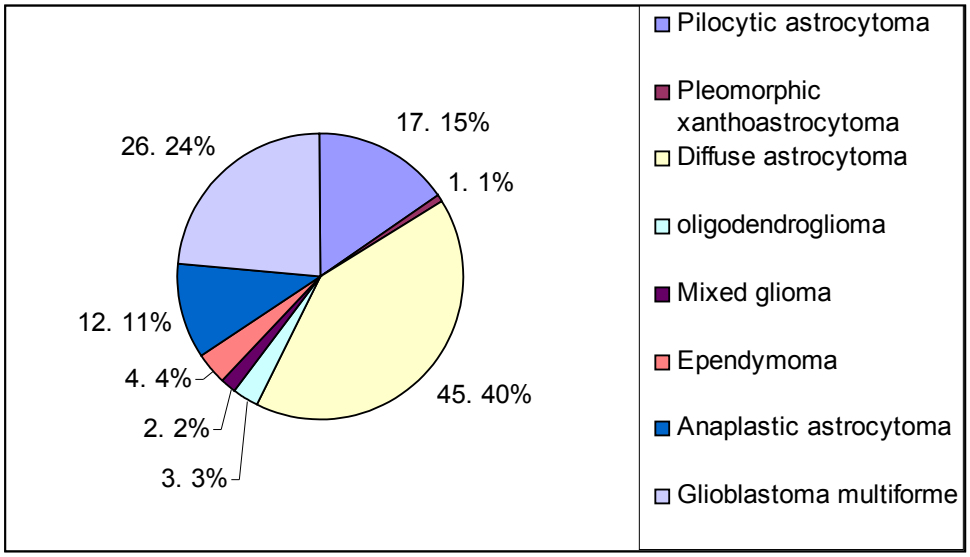
RESULTS AND OBSERVATION

Table – 1: DISTRIBUTION OF THE HISTOLOGICAL VARIANTS OF GLIOMAS

S.No	Histological type	Number of cases n = 110	Percentage (%)
1	Pilocytic astrocytoma	17	15.45%

2	Pleomorphic xanthoastrocytoma	1	0.90%
3	Diffuse astrocytoma	45	40.90%
4	Oligodendroglioma	3	2.72%
5	Mixed glioma	2	1.81%
6	Ependymoma	4	3.63%
7	Anaplastic astrocytoma	12	10.90%
8	Glioblastoma multiforme	26	23.63%

HISTOLOGICAL VARIANTS OF GLIOMAS



S.no	Grade	No of cases (n=110)	Percentage
1	I	17	15.46%
2	II	55	50%
3	III	12	10.91%
4	IV	26	23.63%

Table-2: DISTRIBUTION OF GRADES OF GLIOMAS

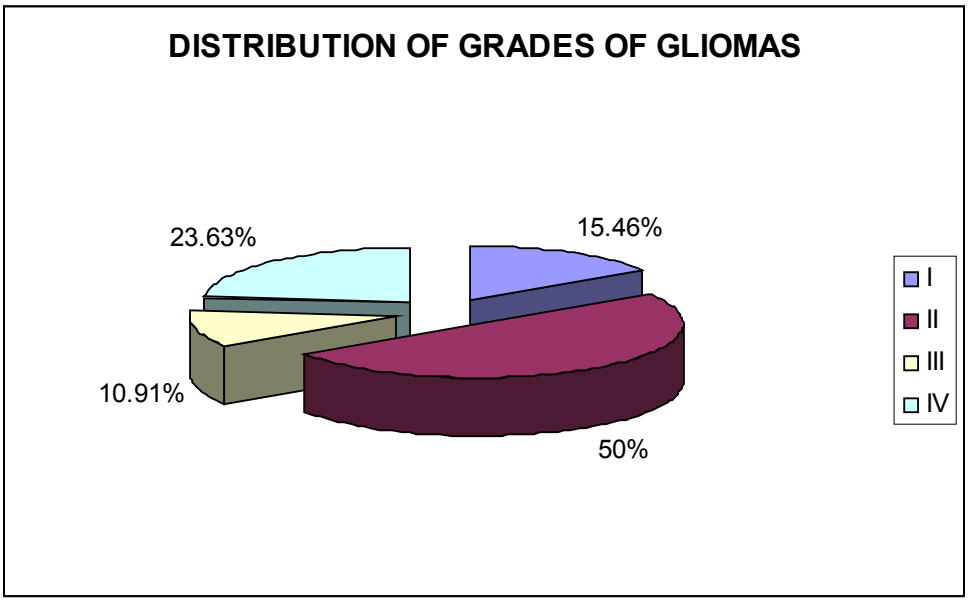


Table-3: SEX DISTRIBUTION

S.No	Tumor	No. of cases	Male	%	Female	%
1	Pilocytic astrocytoma	17	11	64.70%	6	35.29%
2	Pleomorphic xanthoastrocytoma	1	1	100%	-	-
3	Diffuse astrocytoma	45	32	71.11%	13	28.88%
4	Oligodendroglioma	3	2	66.66%	1	33.33%
5	Mixed glioma	2	2	100%	-	-
6	Ependymoma	4	2	50%	2	50%
7	Anaplastic astrocytoma	12	7	58.33%	5	41.66%
8	Glioblastoma	26	16	61.53%	10	38.46%

Table-4: DISTRIBUTION OF GLIOMAS BY LOCATION

S.No	Distribution	Number of cases	Percentage
1	Supratentorial	100	90.91%
2	Infratentorial	10	9.09%

DISTRIBUTION OF GLIOMAS BY LOCATION

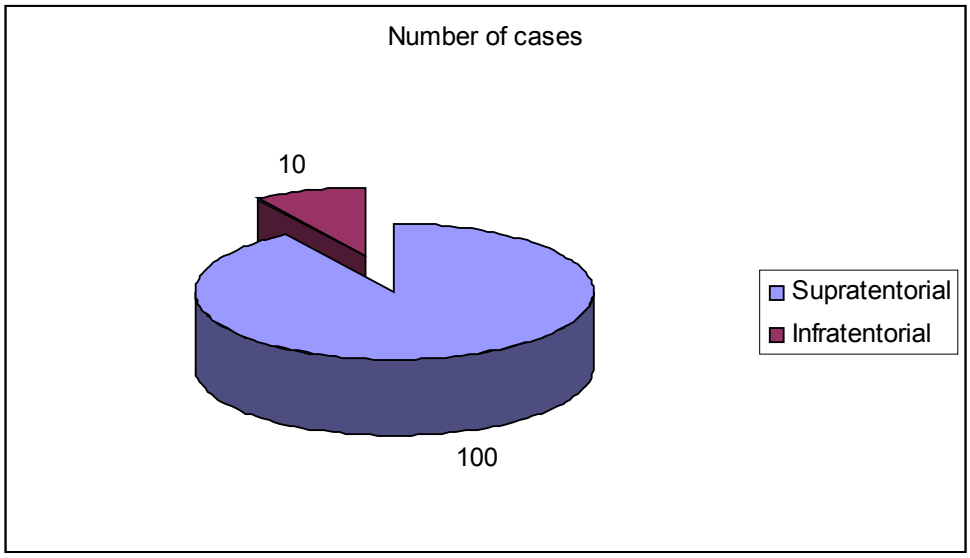


Table-5: AGE DISTRIBUTION

S.No	Age	P.A	P.XA	D.A	ODG	M.G	EPEN	A.A	GBM
1	0-10	9	-	1	-	-	1	-	-
2	11-20	7	1	2	2	-	-	-	1
3	21-30	-	-	17	1	1	1	6	1
4	31-40	-	-	14	-	-	2	2	3
5	41-50	1	-	7	-	1	-	1	7
6	51-60	-	-	4	-	-	-	2	11
7	61-70	-	-	-	-	-	-	1	3

PA : Pilocytic Astrocytoma
PXA : Pleomorphic Xanthoastrocytoma
MG : Mixed glioma
EPEN : Ependymoma

DA : Diffuse Astrocytoma AA : Anaplastic Astrocytoma

ODG : Oligodendroglioma GBM : Glioblastoma Multiforme

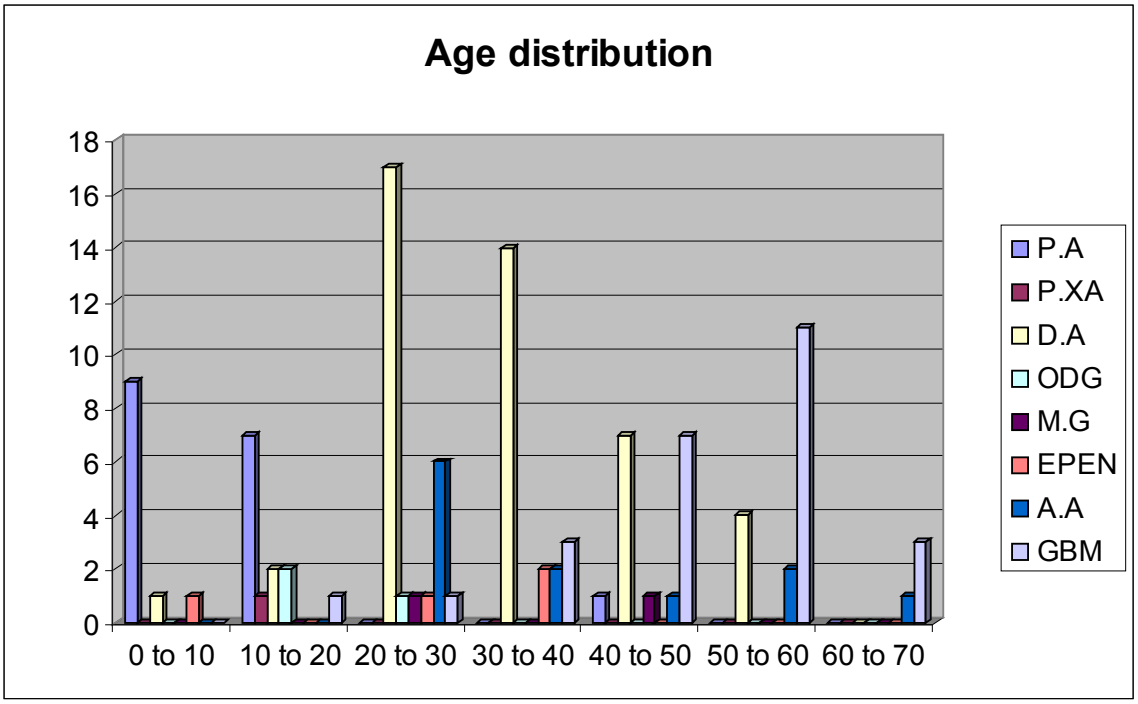


Table – 6: CONTRAST ENHANCEMENT OF GLIOMAS

Glioma grading	Total no. Of cases (n=110)	Nonenhancing		Enhancing	
		No of cases	Percentage (%)	No of cases	Percentage (%)
Grade I	17	14	82.35	3	17.64
Grade II	55	47	85.45	8	14.54
Grade III	12	4	66.66	8	33.33
Grade IV	26	2	7.69	24	92.30

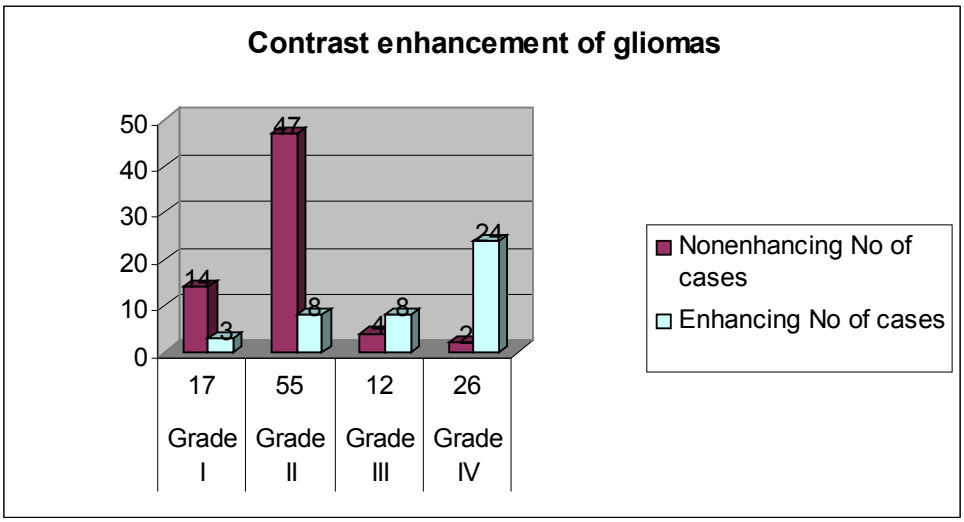


Table-7: MRI SIGNAL CHARACTERISTICS OF GLIOMAS

T1W SEQUENCE

Grade	No. of cases (n=110)	Hypointense	Hyperintense	Heterointense
Grade I	17	15(14.45%)	-	2 (2.55%)
Grade II	55	51(46.75%)	-	4(8.25%)
Grade III	12	11(10.20%)	-	1 (1.8%)
Grade IV	26	17(22.1%)	-	9 (3.9%)

T2W SEQUENCE

Grade	No. of cases (n=110)	Hypointense	Hyperintense	Heterointense
Grade I	17	-	14(13.6%)	3 (3.4%)
Grade II	55	-	51(44%)	4 (11%)
Grade III	12	-	7(9.6%)	5 (2.4%)
Grade IV	26	-	18(20.8%)	8 (5.2%)

DISCUSSION

In our study of 110 patients 72 cases (65%) were low grade and 38 cases (35%) were high grade. The most frequent glioma was diffuse astrocytoma seen in 45 cases (41%) followed by glioblastoma seen in 26 cases (24%). There were 17 cases of pilocytic astrocytoma, 3 cases of oligodendroglioma, 2 cases of mixed glioma, 4 cases of ependymoma and 12 cases of anaplastic astrocytoma. One case of pleomorphic xanthoastrocytoma was reported.

The anatomic location influences the prognosis and treatment of gliomas. Majority of cases were supratentorial and they constituted 91 % (100 out of 110) of total cases studied. 23% of cases were in frontal lobe, 40% were in temporal lobe, 11% in parietal lobe, 3% in occipital lobe and 14% in deeper structures. 10 cases were situated in posterior fossa and all turned out to be low grade gliomas. The statistics were comparable with the study done by Suri Larjavara et al.[48]No differences in location were found among glioblastoma, diffuse astrocytoma and anaplastic astrocytoma.

The most common presenting symptoms were headache associated with nausea and vomiting. 52% of the cases had these symptoms. New onset seizures were the second most common symptoms accounting for 20% of all the cases.

A history of head injury preceding the occurrence of glioma could be elicited in 3 patients. There are numerous anecdotal reports on the occurrence of gliomas after a head injury at the same site. A causal relationship is usually difficult to prove, although an association would be biologically plausible since trauma induces a strong proliferative astrogliosis.[12]

Children in particular presented with seizures more often than any other symptoms. Other symptoms commonly observed were memory

disturbances, slurring of speech, diplopia, blurring of vision and hemiparesis or hemiplegia. These symptoms were observed mostly in the supratentorial gliomas. Some patients experienced drowsiness or were even admitted in a comatose condition.

There were 11 patients who had a previous history of cranial surgery. Two male patients who underwent surgery, followed by radiotherapy for low grade astrocytomas presented with glioblastoma. The remaining 9 patients turned out to be recurrent low grade astrocytoma.

AGE SPECIFIC INCIDENCE:

In our study of gliomas there was a wide age range with the youngest patient being four months of age and the oldest being 75 years old.

Nearly all the pilocytic astrocytomas manifested in children and adolescent before the age of 20 years. The peak incidence was between 8 and 15 years in our study.

Diffuse astrocytomas affected mostly young adults with the peak in the third decade with 17 cases contributing to 37.77% of the cases. The maximum age recorded was in a 58 year old man.

Anaplastic astrocytomas manifested between the third and sixth decade with the maximum age recorded as 65 years.

Glioblastoma multiforme showed a peak incidence between 45 and 70 years with 16 cases falling in this group (61.54%). This finding is comparable with the study conducted by University hospital, Zurich[12] wherein two thirds (67%) of patients fell into this age group.

Oligodendrogliomas were commonly seen between third and fourth decade while ependymomas were reported in children and adults.

Our study showed a gradually increasing age specific incidence from first decade onwards. This peaked in the third decade with 27 cases forming 24.54%. Thereafter the incidence tapered off till the seventh decade which showed only 4 cases constituting 3.63%.

AGE DISTRIBUTION OF GLIOMAS

SEX SPECIFIC INCIDENCE RATES:

Age group (Years)	Number of cases (n=110)	Percentage (%)
0-10	11	10
11-20	14	12.72
21-30	27	24.54
31-40	21	19.09
41-50	16	14.54
51-60	17	15.45
61-70	04	3.63

In our study of 110 cases of gliomas there were 73 males and 37 female patients. The sex specific incidence rate for men was 66.36% and for women was 33.63%. The male predominance was seen in all gliomas irrespective of their age and grade. This corresponds to epidemiological reports from University of Zurich where a male: female ratio of 1.4:1 was observed.

IMAGING STUDIES

LOW GRADE ASTROCYTOMAS

Pilocytic astrocytoma:

Most of the pilocytic astrocytomas were moderately defined and hypodense in plain CT (fig IVa). In our study 3 out of 17 cases of pilocytic astrocytomas showed contrast enhancement (fig IVb). 2 cases in the cerebellum showed mural nodule within cystic areas. 2 cases showed calcifications. Most of the cases were hypointense in T1W and hyperintense in T2W images. Luh GY, Bird CR et al in 1999 showed that typically after intravenous administration of contrast agent there was dense homogenous enhancement of tumor nodule but not of the other walls of the cyst.[30] There were 2 cases in which radiologically appeared to be medulloblastoma turned out to be pilocytic astrocytoma on HPE. Both the cases were located in the

cerebellum. One case of oligodendroglioma and one case of ependymoma diagnosed by CT and MRI studies turned out to be pilocytic astrocytoma on HPE. Hence the sensitivity is 88.23% in diagnosing pilocytic astrocytoma by CT and MRI.

Diffuse Astrocytoma:

Most of the cases displayed no mass effect, no calcification and no hemorrhage (fig Ia). Majority were non-enhancing with contrast while 4 cases showed enhancement (fig Ib). Smirniotopoulus JG et al showed that in low grade astrocytomas the contrast enhancement is usually absent reflecting a lack of tumor vascularity, blood brain barrier breakdown or both.[43] The above character is also noted in our study. All lesions appeared hypointense in T1; most appeared hyperintense in T2 weighted images (fig Ic). Out of the 45 cases of diffuse astrocytomas, 42 cases were reported as low grade gliomas by imaging studies, one case reported as glioblastoma and another case in which the tumor was in posterior fossa reported as hemangioblastoma by CT and MRI turned out to be grade II astrocytoma by HPE. One case of parasagittal lesion in which the differential diagnosis was given as meningioma/tuberculoma ultimately turned out to be diffuse astrocytoma. Hence the sensitivity in reporting diffuse astrocytoma is 93.3% by imaging.

Oligodendroglioma:

In our study all the 3 cases of oligodendrogliomas were hyperdense on plain CT (fig VIa) and showed edema. 2 cases in addition to that showed calcifications (fig VIb). On MRI the lesions were heterointense in T1WI and T2WI due to calcification. The diagnostic accuracy of oligodendrogliomas by imaging modalities in our study is 100%. Among the 2 cases of oligoastrocytomas one case showed calcification and one case enhanced with contrast.

Ependymoma:

Most of ependymomas were mixed to hyperdense on plain CT (fig Va) and 2 cases showed contrast enhancement (fig Vb). Calcification was seen in one case. One case of suprasellar ependymoma was reported as craniopharyngioma by CT and MRI. All the four cases of ependymoma were hypo to heterointense on T1WI and hyper to heterintense on T2WI.

Anaplastic astrocytoma:

The anaplastic astrocytomas were ill defined and exhibited moderate mass effect. In our study 8 out of 12 cases (66.66%) of cases showed contrast enhancement. Calcification and hemorrhage were not seen. In MRI (fig II) almost all cases (11 out of 12 cases) were hypointense on T1W and heterointense on T2W images. One case which showed prominent cystic

changes in CT, reported as low grade glioma turned out to be anaplastic astrocytoma on histopathology.

Glioblastoma multiforme:

All cases of gliblastoma multiforme (n=26) were ill defined in CT, exhibited more mass effect and heterogeneity and more vasogenic edema. All showed areas of necrosis and hemorrhage which were clearly demonstrable in MRI. Calcification was noted in 2 cases. Contrast enhancement was noted in 24 (92.30%) out of 26 cases (P < 0.O1) of glioblastoma, which was moderate to intense (fig III).

Butler AR, Horri SC et al , in their study showed that contrast enhancement of viable tumor including the peripheral rim and the intratumoral solid portions is nearly universal in glioblastoma.

In MRI most lesions (17 out of 26 cases) were hypointense on T1W images and 18 cases hyperintense on T2W images. Out of 26 cases of Glioblastoma 24 cases were diagnosed as glioblastoma and 2 cases were diagnosed as anaplastic astrocytoma by imaging studies. So, the sensitivity in diagnosing glioblastoma by imaging studies is 92.30%.

Patients with nonenhancing high grade astocytomas tended to be younger at presentation. Our results demonstrate that it is important to obtain histologic confirmation of the diagnosis in gliomas regardless of the

presence or absence of contrast enhancement of the tumor on CT, because neither of these characteristics correlates with the tumor histology.

HISTOPATHOLOGY AND GRADING OF GLIOMAS

Our study of 110 gliomas correlating neuroimaging and histology helped us to observe certain microscopic features which enabled us to grade the tumors. Our study determines the effectiveness and the reproducibility of a previously published method of grading gliomas. The main histopathological parameters of importance are histological type and tumor grade.[32]Various grading systems are applied to the astrocytomas which are classified based on the presumed cell of origin. These are then classified according to their degree of malignancy. Widely used grading systems are WHO and St.Anne-Mayo. The main histological signs of malignancy in both systems are nuclear atypia, mitotic activity, vascular proliferation and necrosis. These criteria are interpreted slightly different in these systems. For example a single mitosis is a sign of grade III (Anaplastic) astrocytoma in St. Anne-Mayo's system but higher mitotic activity is a sign of malignancy in WHO 2000 classification.[32]

The WHO classification is more descriptive than St.Anne-Mayo's system, which is based on presence or absence of 4 major criteria.

A similar histological grading system was attempted with oligodendroglioma, but a 4 grade system appears inefficient. Now there are 2 malignancy grades in the WHO classification based on histological parameters similar to astrocytomas.

As shown in Table no-8 features such as cellularity, nuclear atypia, mitosis, giant cells, necrosis and endothelial proliferation were considered.

Table-8: CORRELATION OF HISTOLOGICAL FEATURES WITH GRADING

S.No	Histological Features	No of cases	Low grade (%)	High grade (%)
1	Cellularity Mild to moderate High	 67 43	 61 (91.05) 12 (27.90)	 06 (08.95) 31 (72.09)
2	Nuclear pleomorphism	59	23 (38.98)	36 (61.01)
3	Mitosis	40	07 (17.50)	33 (82.50)
4	Giant cells	14	-	14(100.00)
5	Necrosis	23	01 (04.34)	22 (95.66)
6	Endothelial proliferation	26	-	26(100.00)

Cell density and pleomorphism:

Cellularity is very important in distinguishing reactive gliosis from a true astrocytoma. The criterion used to distinguish cellularity is the presence of inter nuclear space. If the inter nuclear space is less than that of a single nuclear size it means there is dense cellularity. Moreover the nuclear

morphology regarding the variation in size is also important to differentiate neoplasms from gliosis i.e. Since neoplasm's are monoclonal a low grade glioma is usually monomorphous compared to the pleomorphism exhibited by the cells in reactive gliosis. This is applicable only to low grade gliomas.

Very little information is available about cell density and pleomorphism as an independent prognostic factor. In our study, low grade astrocytomas showed mild to moderate cellularity with mild nuclear pleomorphism. All the 3 cases of oligodendrogliomas showed mild to moderate cellularity and mild nuclear pleomorphism. Increased cellularity of oligodendroglioma is related to a worst prognosis.[17]

Table-9 FREQUENCY OF HISTOPATHOLOGIC FEATURES IN HIGH GRADE GLIOMAS

Features	% in high grade lesions (n=38)	% in total (n=110)	"P" value
High cellularity	31 (81.57%)	43(39.09%)	<0.01
Nuclear pleomorphism	36(94.73%)	59(53.63%)	<0.01
Mitosis	33(86.84%)	40(36.36%)	<0.01
Giant cells	36(94.73%)	14(12.72%)	<0.01
Necrosis	22(57.89%)	23(20.90%	<0.01

		)	
Endothelial proliferation	25(65.78%)	25(22.72%)	<0.01

The high grade gliomas (n=38) showed high cellularity (81.75%) and moderate to marked nuclear pleomorphism (94.73%). This showed a "P" value of less than 0.01 which is statistically significant (fig.13).

Mitotic activity:

Presence of mitotic activity is a bad prognostic sign and is valid to all tumours. Many authors use only presence and absence of mitosis. Very little information about influence of mitotic count in the field upon prognosis may be found in references. Sallinen et al researched the number of mitosis in a square millimeter and determined that finding more than 3 mitosis/sq mm has a statistically worse prognosis than fewer mitosis[38]. Other authors suggest that counting mitosis is an unreliable method for it depends considerably upon tissue fixation, processing and upon skills of the pathologist.

In our study mitosis was noted in 40 cases (n=110). Among the 40 cases 33 cases (82.5%) turned out to be high grade gliomas and all of them showed a mitotic count >3/HPF.

Microvascular proliferation:

Microvascular proliferation is formation of multilayered blood vessels from existing capillaries. It plays a large role in tumour growth and spread and is an indicator of a high malignancy grade glioma.

Leon et al have shown that density of microvessels is a prognostic factor of astroglial tumours[29]. In our study endothelial proliferation was noted only in glioblastoma multiforme (fig.16). It was seen in all the 26 cases of glioblastoma. Although in our study endothelial proliferation was noted only in high grade gliomas, it has been mentioned in literature[32] that rarely endothelial proliferation can be seen in pilocytic astrocytoma (WHO Grade 1).

Giant cells:

The presence of giant cells in histology is a feature of a high grade neoplasm mostly. This was observed in our study wherein all 14 cases (100%) of glioblastoma showed giant cells (fig.16) and were associated with features of endothelial proliferation and necrosis.

According to Jellinger the frequent occurrence of giant cells as well as regressive changes with necrosis and vascular responses are indirect indicators of malignancy which coincide with histochemical and biochemical data.[23]Schmidt and Urban et al in their study showed that giant cells in glioblastoma multiforme indicate a better prognosis.

Necrosis:

Necrosis is a distinguishing indicator of glioblastoma multiforme. It is incompatible with a diagnosis of anaplastic astrocytoma,though it may be present in anaplastic oligodendrogliomas and oligoastrocytomas.[32] Necrosis is a sign of bad prognosis. The pattern of necrosis may be either geographic or palisading type.

Necrosis as a feature of high grade malignancy has to be evaluated with great care as we have seen in our study that one case with necrosis proved to be a low grade glioma. Most often necrosis is associated with grade IV glioma (fig.14) as the percentage of high grade gliomas with necrosis in our study was 95.65%.

Calcification:

The presence of calcification in 9 out of 110 cases of gliomas represents an incidence of 8.18%. Calcification was seen in 66.66% of oligodendrogliomas, 4.76% of low grade gliomas and 11.5% of high grade gliomas. In low grade gliomas the incidence of calcification tended to be higher in young males.

Tanaka Y et al found that only in astrocytomas both the duration of symptoms and the post operative survival time of the calcified cases were longer than those of the uncalcified. In conclusion that it is not the

histological type but duration of the clinical course that plays a more important role in calcification of gliomas.[49]

SUMMARY

The present study included 110 cases of gliomas resected during the period from. May 2005 to August 2007.

The salient features observed in this study are:

1. The most frequent glioma was Grade II astrocytoma seen in 45 cases (41%)

   followed by Grade IV astrocytoma seen in 26 cases (24%).

2. The age group affected ranges from 4 months old infant to

   75 years with a mean age of 38 years.

3. Of 110 cases in the study, males constituted 73 cases (66.36%) and females 37 cases (33.63%).

4. The peak incidence was in the third decade with 27 cases constituting 24.54% of the total number of cases.

5. The most common site in the present study was the temporal lobes with 44 cases, followed by the frontal lobes with 25 cases.
6. Infratentorial gliomas which are considered rare tumours accounted for 9% of the cases.
7. The most common presenting symptoms were headache associated with nausea and vomiting. Recent onset seizures were the next most common symptom.
8. Non enhancing gliomas were malignant in 6 out of 38 cases of high grade astrocytomas (15.78%) especially in older patients. Therefore histologic confirmation of the diagnosis is important in all patients suspected of harboring a primary glial neoplasm.
9. WHO grade II gliomas formed the overwhelming majority with 55 cases forming 50% of total. Grade I gliomas numbered 17 forming 15.46% while grade III and grade IV constituted 10.9% and 23.63% respectively.
10. Most of the grade II astrocytomas were diffuse astrocytomas forming 45 out of 55 cases (40.9%).
11. One of our case was a rare variant of grade II glioma namely pleomorphic xanthoastrocytoma (n=1).

CONCLUSION

From our study we observe that non – enhancement of gliomas does not equate with low – grade malignancy. This fact should be taken into account when biopsy and treatment are being planned in patients with nonenhancing brain tumors.

The diagnosis of gliomas has always depended upon conventional histo-morphological study of H & E stained sections. The prognosis and response to treatment of the various types of gliomas correlates well with the present WHO grading system. Ancillary techniques like immunohistochemistry and electron microscopy are usually not required unless the tumor is very undifferentiated and anaplastic.

A lot of research is being done with reference to gliomas and a whole host of new molecular targets like bcl–2 etc have been discovered. The future holds promise that gliomas may be treated by non invasive methods like targeted molecular therapy.

Although current emphasis is more on molecular, genetic and immunohistochemical research, the principal reliable morphologic prognostic criterion – histologic grade of malignancy – still remains and is applied in clinical practice.

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